A New Orally Active Quaternary Ammonium, Ganglion Blocking Drug Capable of Reducing Blood Pressure, SU-3088

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Experiments were performed in animals to evaluate 4,5,6,7-tetrachloro-2-(2 dimethylaminoethyl)-isoindoline dimethochloride, (Su-3088), as an orally effective ganglion blocking drug. These demonstrated reduction of blood pressure, suppression of vasopressor reflexes and potentiation of the pressor action of epinephrine. Neostigmine deblocked drug effects and returned responses toward normal. Experiments in patients produced reduction of blood pressure, warming of extremities and delay of gastric emptying. Preliminary trial as a treatment for hypertension suggested that the drug may be useful. It has a long period of action, 12 hours or more and a small dose requirement, 50 to 100 mg.

Of many ganglion blocking agents developed since tetrathyllammonium chloride only two have been sufficiently active with oral administration to justify extensive clinical use. These are hexamethonium bitartrate or chloride and pentolinium tartrate (Ansolyn). Each is a symmetrical compound having six and five carbon chains respectively. A new compound prepared by Huebner and reported by Plummer, Trapold, Schneider and Earl \(^2\) differs in that it is unsymmetrical and has two carbon atoms separating the quaternary nitrogen groups. The compound (fig. 1) is 4,5,6,7-tetrachloro-2-(2 dimethylaminoethyl)-isoindoline dimethochloride.* Plummer demonstrated its ganglion blocking action, found its duration of action twice as long as that of hexamethonium or pentolinium and demonstrated efficient oral activity in dogs. This report describes experiments in dogs to test the ganglion blocking action; it also presents the first clinical testing in man and trial in hypertensive patients.

Experiments in Dogs

Seven acute experiments were performed in dogs weighing 11 to 25 Kg, anesthetized with chloralose, 0.1 Gm. per kilogram, given intravenously. A tracheal cannula was inserted, the carotid arteries isolated, and the vagus nerves divided. The right femoral artery was divided and cannulated proximally. This permitted recording of mean systemic blood pressure, using a mercury manometer.

Respirations were measured by a pneumograph connected to a recording tambour.

After preparation, standard tests of the circulatory system were employed in each animal. Carotid sinus reflexes were elicited by occlusion of both common carotid arteries, using bulldog clamps applied for one minute. Peripheral vagal stimulation was accomplished for 15 seconds, using a tetanizing current from a Harvard inductorium set at 7 or 8 cm. Central vagal stimulation also employed a tetanizing current for 15 seconds but the setting of the inductorium was reduced to 6 or 7 cm. Epinephrine was injected as a 1:10,000 solution through a venous cannula, one gamma per kilogram.

Results

The typical effects of a single injection of Su-3088, 2 mg. per kilogram, are shown in figure 2. Increments up to 2 mg. per kilogram were additive. Additional doses beyond this amount did not significantly enhance any effect. Neostigmine elevated blood pressure and restored pressor reflexes and the cardiac slowing with stimulation of the peripheral vagus. Results of each test are summarized.

Potentiation of Epinephrine. Increase of blood pressure caused by injection of one gamma of epinephrine was measured before and after 2 mg. per kilogram of Su-3088 in four dogs and after 1 mg. per kilogram in three. With 2 mg.

\(^*\) Supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

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4,5,6,7-TETRACHLORO-2-(2-DIMETHYLAMINOETHYL)-ISOINDOLINE
DIMETHOCLORIDE

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{CH}_2 \quad \text{CH}_2 \\
\text{N}(\text{CH}_2)_2 \quad \text{N}(\text{CH}_2)_2 \\
\text{Cl} \quad \text{Cl}
\end{array}
\]

(Chloride)

**Su-3088**

Fig. 1. Chemical name and structural formula of Su-3088.

per kilogram the average of the rise of blood pressure before the Su-3088 was 72 mm. Hg, mean systolic, above a general blood pressure level of 130 mm. After the drug the rise was 85 mm. Hg above a level of 101 mm. The average increase of the height of the rise after the drug was 13 points and the average reduction of general blood pressure level was 29 points. After 1 mg. per kilogram such potentiation was evident in only one of the three dogs. With subsequent doses greater than 2 mg. per kilogram there was no additional increase of the pressor response to epinephrine and no further decrease of general blood pressure.

**Carotid Sinus Reflex.** The average increase of mean systolic blood pressure with occlusion of both carotid arteries before Su-3088, 2 mg. per kilogram, in four dogs was 51 mm. above a general blood pressure level of 108. After the drug the average increase was 14 mm. above a level of 73 mm. Hg. The average increase before a dose of 1.0 mg. per kilogram in three dogs was 99 mm. above a level of 159 mm. After this dose the increase was 19 mm. above a level of 113 mm.

**Stimulation of Central Vagus.** The pressor response with stimulation of the central end of one divided vagus nerve was similarly measured. Before 2 mg. per kilogram the average rise was 58 mm. above a level of 128 mm., afterward 23 mm. above a level of 73 mm. The rise decreased 35 mm. and the blood pressure decreased 55 mm. after the drug. With 1 mg. per kilogram the average rise before the drug was 47 mm. above 137 mm. and after the drug the rise was 39 mm. above 115 mm., a lessening of the rise by 8 mm. and of the blood pressure level by 42 mm.

**Blood Pressure and Pulse Decrease with Stimulation of the Distal End of the Divided Right Vagus.** Four dogs were tested before and after Su-3088, 2 mg. per kilogram. The average blood pressure fell from 130 mm. to 29 mm. before the drug and from 122 mm. to 106 mm. afterward. The average pulse decreased from 192 per minute to 0 to 4 beats in 15 seconds before the drug and from 136 per minute to 124 per minute afterward. Three dogs were tested before and after 1 mg. per kilogram. The average blood pressure fell from 124 mm. to 32 mm. before the drug and from 78 mm. to 61 mm. afterward. The average pulse decrease was from 153 per minute to 0 to 12 beats in 15 seconds before the drug and from 139 to 108 per minute afterward.

**Blood Pressure and Pulse.** Pulse and blood pressure were selected from the kymograph record at a level point not associated with any stimulus, before and after Su-3088. For four dogs given 2 mg. per kilogram the mean systolic systemic blood pressure averaged 127 mm. Hg before and 100 mm. afterward, pulse 185 per minute before and 133 afterward. For three dogs receiving 1 mg. per kilogram pressure changed from 166 mm. to 113 mm. and pulse from 188 per minute to 136.

**Accumulating Doses.** Of the seven dogs studied three were given single doses of Su-3088, 1.0 mg. per kilogram and then neo-stigmine. Four received repeated and progressively increasing doses to a total of 2.5, 8.5, 8.9 and 9 mg. per kilogram. None exhibited curariform or other toxic effects. Supply of the drug was not enough to test larger doses. Initial injections of 0.5, 1 and 2 mg. per kilogram produced prompt reductions of blood pressure of 30 mm. Hg or more. This reduction persisted during three to five hours of observation unless neostigmine was used. Smaller initial doses, 0.001 to 0.05, caused no appreciable effect. Doses of 0.05 mg. per kilogram caused slight reduction of pressure and lessening of the cardiac slowing of stimulation of the peripheral vagus. After a dose of 1 or 2 mg. per kilogram, additional doses of 2 to 5 mg. per kilogram produced slight, transient or no further
reduction of general blood pressure, block of reflexes or potentiation of rise with epinephrine.

Neostigmine Debloking Effect. Neostigmine methylsulphate was given intravenously, 0.5 mg. to one dog and 1 mg. to another, at the end of two experiments following total accumulative doses of 8.5 mg. per kilogram and 9 mg. per kilogram of Su-3088. General blood pressure promptly rose 30 and 36 mm., slightly exceeding the blood pressure at the start of the experiment. Return of cardiac slowing and of rise with pressor reflexes occurred promptly, responses equalling or exceeding those during the control period at the start of the experiment. The rise with epinephrine continued with little change.

Initial doses of 1.0 mg. per kilogram of Su-3088 were given to three dogs 43 to 55 minutes before intravenous administration of 0.25, 0.5 and 0.5 mg. doses of neostigmine methylsulphate. No additional drugs were then given. Reflexes and cardiac slowing depressed by Su-3088 immediately returned toward normal following neostigmine and the general blood pressure level returned toward its original height. Rise with epinephrine continued higher than before the Su-3088, equal to the potentiation after Su-3088. Following the neostigmine, reflexes and epinephrine were tested at intervals during 150 to 228 minutes. Toward the end of this time period, reflexes were again diminishing in two dogs and were blocked in the third. This evidently represented a wearing off of the neostigmine deblocking effect and a return of the long-lasting blocking effect of the Su-3088. A final dose of neostigmine, 0.25 mg. to 0.5 mg., was then given and restored reflexes to or almost to the original responses, those of the control period before Su-3088.

Tests in Man

Single oral doses of 50 or 100 mg. of Su-3088 have been given to 18 patients on a fasting stomach at 8:30 or 9:00 a.m. Blood pressures with the patient in the supine and also in the upright position were obtained at intervals of 5 to 30 minutes before and for 29 hours after the drug, using a cuff-mercury sphygmomanometer. Pulse and respiration rates were counted. Skin temperature readings were obtained from the umbilicus to toe several times before and during six hours after the drug. Occurrence of side actions such as dilatation of the pupils and dryness of the mouth were noted. Some patients were also given barium by mouth an hour after the drug or several hours afterward and progress of emptying of the stomach was determined by hourly roentgenograms for six hours.

Results:

Blood Pressure. Three normotensive individuals were given Su-3088 orally. One received a 50 mg. dose. Control readings of blood pressure ranged around 100/70 supine and 105/74 standing. Three and a half hours after the drug the supine pressure was 94/72 and the
upright pressure was 88/70. There was minimal blurring of vision and dryness of mouth. Two normotensive individuals were given 100 mg. of Su-3088 orally. They had more pronounced blurring of vision and dryness. Blood pressure in the supine position reduced from 120/74 and 110/60 to 80/70 and 84/54, respectively, reaching their lowest level at about six hours. Postural hypotension prevented standing at three to six hours and this persisted into the night. Temperature of the toes increased. Rate of pulse and respiration did not change.

Eight hypertensive patients were given 100 mg. of Su-3088 orally. One had no significant reduction of blood pressure and did not develop postural hypotension. This patient was one known to tolerate 600 mg. doses of pentolinium four times a day without reduction of blood pressure or blurring of vision. He is an example of the occasional patient who resists or poorly absorbs quaternary ammonium compounds. An injection of 110 mg. of Su-3088, 2 mg. per kilogram intravenously, produced marked blurring and postural hypotension but no reduction of supine blood pressure.

A second of the eight patients receiving 100 mg. doses had a severe hypertension and a marked cirrhosis of the liver. Subsequently he could not be managed on continuing treatment because of fluctuations of pressure every 8 to 12 hours, periods of elevation to 220/125 alternating with periods of decrease to 130/90 and postural weakness when the pressure was low. Because of the uncertainties related to his cirrhosis and the use of a new drug, treatment was discontinued. With the first test dose his supine blood pressure reduced from 190/120 to 148/96 for 12 hours, upright pressures reduced to 110/90 and blurring of vision developed.

The remaining six patients continue using Su-3088, a single dose of 75 or 100 mg., an hour before breakfast. The initial effect of the test 100 mg. dose for each is shown in figure 3. The supine blood pressure of one patient rose during the first three hours after the drug. His subsequent pressures and those of the other

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**Su 3088, 100 Mg. ORALLY-(PATIENT SUPINE)**

![Graph](http://circ.ahajournals.org/)

**Fig. 3.** Effect of ingestion of 100 mg. of SU-3088 on the supine blood pressure of six patients. Reduction of pressure persisted 12 to 29 hours.
patients remained reduced for 12 to 20 hours. Each patient was unable to stand for several hours. Development of postural hypotension is shown in figure 4. During 8 to 16 hours thereafter these patients were unable to stand any length of time without syncope. Fourteen to 21 hours after the drug they still had some postural hypotension.

Seven hypertensive patients were given test doses of 50 mg. of Su-3088 orally. One had no significant reduction of blood pressure or blurring of vision. He subsequently required 200 mg. before side actions and reduction of pressure occurred. This is another example of a patient who resists or poorly absorbs the drug.

A second of the seven patients receiving a 50 mg. test dose also had a severe hypertension with fluctuations of blood pressure on treatment, depressions to around 170/100 lasting five to nine hours alternating with periods of elevation to around 220/130. She finally became stabilized at pressures around 180/124 on two doses a day, 100 mg. an hour before breakfast and 100 mg. an hour and a half after the evening meal. Postural hypotension occurred and persisted throughout her eight days of hospitalization but was not disabling. The first 50 mg. dose produced postural hypotension within 45 minutes. However, the supine pressure which was 212/114 during the control period rose during the first two hours after the drug to a high of 260/155, then reduced to 160/100 for 12 hours.

Five of the seven patients receiving 50 mg. test doses of Su-3088 continue on satisfactory management, using Su-3088, 50 to 75 mg. single doses an hour before breakfast. Each had a mild hypertension which had reduced with rest. Their blood pressures during the control period ranged from 140/80 to 180/96. After the 50 mg. oral dose the pressure ranged from 130/65 to 144/90 lying. Blood pressures in two patients in the erect position were 104/72 and 100/68 five hours after the Su-3088. Pressures were too low to read in three patients since they could not stand without fainting. Hypotensive effects continued during the night and some postural hypotension persisted the next morning.

Pulse and Respiration. For the six hypertensive patients receiving 100 mg. test doses of Su-3088 the rate of pulse and respiration averaged 68 and 18 during the control period, 75 and 15 an hour after the drug, 76 and 18 at four hours. For the five receiving 50 mg. test doses the averages were 72 and 16, 74 and 16, and 87 and 16. The highest pulse reading of any patient during the period of hypotension was 100, the lowest 56. One patient exhibited slowing of respiration from 24 to 10 with return to 18 at four hours.

Skin Temperature of a Leg. Four hypertensive patients receiving a 100 mg. test dose orally had measurements of skin temperature from the umbilicus to the great toe. Room temperature ranged from 26 to 27 C. through the test period. The average gradient, umbilicus to great toe, during the control period was 6.5 C. The gradient decrease 1 to 3.2 degrees a
half hour after the drug, 1.1 at one hour, minus 0.1 at two hours, 0.2 at three hours and 0.2 at five hours. Three patients had measurements before and after the 50 mg. oral test doses. The control gradient average was 5.1 degrees. One hour after the drug the average was 2.3, three hours afterward 1.3 and at five hours it was 1.3. In each group of patients dryness and warmth of the skin was still evident at bedtime, 12 to 15 hours after the drug.

**Gastric Empting.** Roentgenograms were obtained at hourly intervals for five or six hours following ingestion of barium. The barium was given one hour after ingestion of Su-3088. A light meal was given three hours after the barium. Five patients had received a 100 mg. dose orally. In four, delay of emptying of the stomach caused retention of the barium from 100 per cent to 95 per cent one hour after the barium and two hours after the drug. Delay continued through six hours at which time retention was 80 to 100 per cent. A typical series of roentgenograms is reproduced in figure 5. The fifth patient emptied relatively normally, 60 per cent, 40 per cent, 40 per cent, 30 per cent, 10 per cent and at six hours there was only a trace of barium in the stomach.

Six patients received a 50 mg. dose orally. In five delayed emptying of the stomach caused retention of barium of 95 to 100 per cent at one hour, retention persisting through five or six hours at 85 to 100 per cent. The sixth patient had only 30 per cent at one hour and 10 per cent at two hours. The stomach had emptied normally within three hours. Roentgenograms obtained 24 hours after the drug in three of these patients with delayed emptying revealed barium in the right colon in two and in the lower small intestine and right colon in the third.

Four patients were given barium five to eight hours after the morning dose. They had taken breakfast and lunch. Barium was ingested and films were obtained at hourly intervals starting an hour or two after lunch. One patient emptied rapidly, there being 10 per cent retention an hour after the barium and six hours after his morning dose of 50 mg. of Su-3088. Another patient who had taken a 50 mg. dose nine hours before his roentgenograms had 98 per cent retention one hour after barium, 95 per cent the next hour and 80 per cent an hour later. One who had taken 75 mg. before breakfast seven hours before his roentgenograms had 95 per cent retention one hour after barium and then 90 per cent and 90 per cent. The fourth patient had taken 100 mg. eight hours before his roentgenograms and had 100 per cent retention an hour after barium, 100 per cent an hour later and 100 per cent at the next hour.

**Side Actions.** Effects on the pupils, salivary glands, bowel movements, urinary bladder and blood pressure with upright posture were described by patients as blurring of vision or photophobia, dryness of mouth, constipation, decreased force of micturition, and dizziness or weakness when standing. These actions of the drug are the effects reported upon the last observations by 11 patients after three to six weeks of treatment and relate to their present dosage schedule, 50, 75, or 100 mg. one hour before breakfast. Side actions of the drug are evident a half hour to an hour and a half after ingestion.

Five patients are taking 50 mg. doses each morning. One cannot read for eight hours. Another has some difficulty in reading for 16 hours. Another has photophobia for five hours. The remaining two have a little difficulty for only two hours. Dryness of mouth is slight in four patients and no dryness is noted by the fifth. Two patients notice a little decrease of force of micturition in the morning. Each patient has experienced weakness with standing lasting most of the day and occurring once or on two or three separate days since starting the drug. Bowel movements occur spontaneously early each morning in four patients and every other morning in the fifth who takes a laxative once a week.

Three patients are taking 75 mg. doses each morning. One cannot read for five hours, two can read but one notices blurring for nine hours and the other photophobia for 10 hours. Dryness of the mouth is slight and no decrease of force of micturition is observed. Each patient notices postural weakness at times in the morning and occasionally sits down or lies down for a few minutes. Bowel movements
occur each morning in two patients and evening and morning in one. Each takes prune juice, mineral oil or cascarilla.

Three patients are taking a 100 mg. dose each morning an hour before breakfast. Two cannot read for 12 to 14 hours and are advised to obtain positive correction lenses. One has blurring of vision lasting an hour each morning. Each notices some dryness of the mouth in the morning, little or none in the afternoon. Slowness of the bladder is not noticed. Weakness or dizziness is noticed for one to three hours each morning by two and for a day on two occasions by the third.

**Discussion**

Su 3088 was developed as a results of experiments by Plummer, Trapold, Earl and Schneider in which a group of bis-quaternary derivatives of dialkyl-amino-alkyl isoindolines were compared for ganglion blocking activity. They found that maximum ganglion blocking potency and maximum oral absorption were associated with interposition of two carbon atoms between quaternary ammonium centers, also with alkylation and quaternization by methyl groups. This led to synthesis of Su-3088. Orally in unanesthetized dogs a dose of 2 mg. per kilogram produced maximum relaxation of nictitating membranes followed by a 50 per cent recovery at 8 to 10 hours and complete recovery at 18 to 20 hours. Decrease of blood pressure occurred and roughly paralleled ganglion blocking activity. Our experiments in anesthetized dogs confirm the ganglion

![Roentgenograms at hourly intervals after barium](image)

**Fig. 5.** Hourly roentgenograms starting two hours after taking 100 mg. of SU-3088 orally and one hour after ingestion of barium. Between the third and fourth film a light meal was taken. Delay of rate of gastric emptying was still evident at six hours.
blocking actions of Su 3088 and the long duration of action.

Certain of the pharmacological observations have important therapeutic implications. The effective dose intravenously for the dog is 1 to 2 mg. per kilogram. The dose we have found effective in man is similar, 50 to 100 mg. per patient. Absorption is apparently efficient. In the dog and apparently also in man repeated smaller doses add their effects until the optimum dose is reached. After 2 mg. per kilogram, additional doses do not significantly add to reduction of blood pressure or to other actions of the drug. Patients given additional doses of 50 or 100 mg. during the first 10 hours after an effective dose have no increase of hypotension or of side actions. In dogs and in man, reduction of blood pressure in the supine position is to levels around 100 mm. Hg; reduction does not progress to the 80 mm. or lower levels associated with cord section or shock. Patients are comfortable in the supine position even though reduction has occurred from high levels of pressure. This drug evidently has an inherent safeguard in that it suppresses vasopressor reflexes and reduces supine blood pressure to or toward normal without causing troublesome hypotension in the supine position, even with doses which exceed the effective dose.

Two other observations have important therapeutic implications. One is that neostigmine after Su-3088 deblocks ganglia for the duration of the period of action of the neostigmine which is two hours or more. It would not seem logical to recommend neostigmine each morning for bowel movements as is now done for another ganglion blocking drug, pentolinium. All quaternary ammonium compounds tested since our original observation of deblocking effect of Banthine has been deblocked with neostigmine. The second observation is that the typical potentiating effect of the ganglion blocking drug on the pressor effect of epinephrine might explain fluctuations of blood pressure. Occasional rises of pressure are observed on continuing treatment with hexamethonium, pentolinium or Su-3C88 and could be explained by the unopposed or increased effectiveness of spontaneously secreted adrenalin. Concomitant use of an adrenolytic drug is under trial.

Testing and clinical trial in 18 patients has demonstrated that Su-3088 causes reduction of supine blood pressure without tachycardia, development of postural hypotension, warming of extremities, mydriasis, decrease of rate of emptying of the stomach and other evidences of partial to complete blockade of ganglia of the sympathetic and parasympathetic division of the autonomic nervous system. Effects develop an hour or more after 50 to 100 mg. doses orally, reach a maximum at six to eight hours, are usually diminishing by 12 to 16 hours and are no longer evident at 24 hours. Constipation, decrease of force of micturition and dryness of the mouth have occurred infrequently or to a minor degree. Delay of emptying of the stomach caused nausea and emesis in four patients receiving their first dose and on one or two other occasions during the first several days of continuing treatment. Otherwise meals were ingested without symptoms. This delay of gastric emptying is an important consideration in planning the timing of subsequent doses since medicine is usually absorbed only when it reaches the intestine. Plummer has found that Su-3088 is stable in gastric juice. Doses given while the stomach is emptying slowly would be slowly absorbed without reaching a high peak blood level. The first dose of the day should be given before breakfast for a good peak level and a maximum blockade. After trying doses before, with and after breakfast it was found that use of the drug an hour before breakfast allows the most accurate adjustment.

Little can be said at the present time concerning results in the 16 patients with hypertension who are now on continuing treatment for three to six weeks. No toxic effects have been observed. Twelve had been taking effective doses of hexamethonium chloride orally. Relief of symptoms has equalled that of hexamethonium and two patients who had experienced some headache in the morning now have none. Each of the 12 prefers Su-3088 for reasons varying from relief of constipation to need to take fewer tablets a day. The greatest
difficulty has been the blurring of vision which may last all day long in some patients even with 50 mg. doses. Postural hypotension is usually present and may be troublesome in the morning. The supine blood pressure is usually reduced. However, even on a standard morning dose the effects may be more pronounced on some days than on others. Each patient has had occasional high and occasional low readings of blood pressure both supine and standing. Trial of use of two or three doses a day has been possible for only a few days because of inadequate supply of the drug.

Results at present seem to indicate that control of blood pressure has been a little more consistent than with pentolinium; certainly effects continue longer and fewer milligrams are required each day. Side actions and variations of effect are similar. It is not yet certain whether a schedule of therapy can be worked out for Su-3088 which will achieve results comparable to those we have obtained with hexamethonium, given orally, for four years. At least this new drug should be a useful addition to the agents now available for control of hypertension and the reduced milligram requirement and decrease in number of tablets needed each day should predict a financial saving for patients.

SUMMARY

Su-3088 is an orally active ganglion blocking agent capable of suppressing pressor reflexes, reducing blood pressure in the supine position and producing postural hypotension for 12 or more hours after the ingestion of a small dose, 50 to 100 mg.

SUMMARIO IN INTERLINGUA

Esseva executate experimentos animal pro evalutar le efficacia ganglioblocante de 4, 5, 6, 7-tetrachloro-2-(2 dimethylaminoethyl)-isoindo-lina-dimethochlorido (SU-3088) in administration oral. Le experimentos demonstrava un reduction del pression sanguinee, suppression del reflexos vasopressor, e potentiation del action pressorial de epinephrina. Neostigmina dislocava le effectos del droga e re-establiva le normal del responsas. Experimentos con humanos produceva reduction del pression sanguinee, calefaction del extremitates, e retardation del vacuacion gastric. Essayos preliminari in le tractamento de hypertension pare indicar que le droga pote esser de valor in iste campo. Su action es longeve—12 horas o plus—e illo require parve dosages—50 a 200 mg.

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A New Orally Active Quaternary Ammonium, Ganglion Blocking Drug Capable of Reducing Blood Pressure, SU-3088
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